# Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction

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Abstract: Aims To evaluate safety and effectiveness of early generation drug-eluting stents (DES) compared with bare-metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), and to determine whether benefits and risks vary over time. Methods and results We performed a meta-analysis of 15 randomized controlled trials enrolling a total of 7867 patients comparing first-generation FDA-approved DES with BMS in patients with STEMI. Random effect models were used to assess differences in outcomes between DES and BMS among different time periods with regard to the pre-specified primary outcomes stent thrombosis (ST) and target vessel revascularization (TVR). The overall risk of definite ST was similar for DES and BMS [risk ratio (RR) = 1.08, 95% CI 0.82-1.43]. However, there were time-dependent effects, with a RR of 0.80 during the first year (95% CI 0.58-1.12) and 2.10 during subsequent years (95% CI 1.20-3.69), with a positive test for interaction between RR of ST and time (P for interaction = 0.009). Results were similar for definite or probable ST (P for interaction = 0.015). In the overall analysis, TVR was performed less frequently in patients with DES when compared with BMS (RR 0.51, 95% CI 0.43-0.61), with a greater benefit in the first year (RR 0.46, 95% CI 0.38-0.55) when compared with subsequent years (RR 0.75, 95% CI 0.59-0.94; P for interaction = 0.007). Conclusion An early benefit of early generation DES in primary PCI for STEMI with a reduction in TVR and a trend towards less definite ST is offset in subsequent years by an increased risk of very late ST

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# Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction

**Bindu Kalesan[1,2,3†], Thomas Pilgrim[1†], Katja Heinimann[3], Lorenz Räber[1,4], Giulio G. Stefanini[1], Marco Valgimigli[5], Bruno R. da Costa[3], François Mach[6], Thomas F. Lüscher[7], Bernhard Meier[1,2], Stephan Windecker[1,2], and Peter Jüni[2,3*]**

[1]Department of Cardiology, Bern University Hospital, Bern, Switzerland; [2]Clinical Trials Unit, University of Bern, Bern, Switzerland; [3]Institute of Social and Preventive Medicine, University of Bern, Switzerland; [4]Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; [5]Department of Cardiology, University Hospital of Ferrara, Italy; [6]Department of Cardiology, University Hospital of Geneva, Switzerland; and [7]Department of Cardiology, University Hospital of Zurich, Switzerland

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**Aims** To evaluate safety and effectiveness of early generation drug-eluting stents (DES) compared with bare-metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), and to determine whether benefits and risks vary over time.

**Methods and results** We performed a meta-analysis of 15 randomized controlled trials enrolling a total of 7867 patients comparing first-generation FDA-approved DES with BMS in patients with STEMI. Random effect models were used to assess differences in outcomes between DES and BMS among different time periods with regard to the pre-specified primary outcomes stent thrombosis (ST) and target vessel revascularization (TVR). The overall risk of definite ST was similar for DES and BMS [risk ratio (RR) = 1.08, 95% CI 0.82–1.43]. However, there were time-dependent effects, with a RR of 0.80 during the first year (95% CI 0.58–1.12) and 2.10 during subsequent years (95% CI 1.20–3.69), with a positive test for interaction between RR of ST and time (*P* for interaction = 0.009). Results were similar for definite or probable ST (*P* for interaction = 0.015). In the overall analysis, TVR was performed less frequently in patients with DES when compared with BMS (RR 0.51, 95% CI 0.43–0.61), with a greater benefit in the first year (RR 0.46, 95% CI 0.38–0.55) when compared with subsequent years (RR 0.75, 95% CI 0.59–0.94; *P* for interaction = 0.007).

**Conclusion** An early benefit of early generation DES in primary PCI for STEMI with a reduction in TVR and a trend towards less definite ST is offset in subsequent years by an increased risk of very late ST.

**Keywords** Early generation drug-eluting stents (DES) • Bare-metal stents (BMS) • ST-segment elevation myocardial infarction (STEMI) • Stent thrombosis (ST)

## Introduction

In patients with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) decreases infarct size and rates of re-infarction, and improves survival compared with fibrinolysis.[1] Bare-metal stents (BMS) reduce the risk of re-occlusion and re-infarction after PCI,[2,3] whereas early generation drug-eluting stents (DES) further decrease the risk of restenosis and target lesion revascularization without increasing the incidence of death or myocardial infarction in a broad spectrum of patients, including STEMI.[4,5] However, there is a higher risk of late and very late stent thrombosis (ST) associated with DES when compared with BMS,[6] which is more pronounced in patients with STEMI than in patients with stable

† B.K. and T.P. contributed equally to this work.

* Corresponding author: Division of Clinical Epidemiology & Biostatistics, Institute of Social and Preventive Medicine, University of Bern, 3012 Bern, Switzerland. Tel: +41 31 631 33 78, Fax: +44 31 631 35 20, Email: pjuni@ispm.unibe.ch

coronary artery disease.[7,8] In autopsy specimens of lesions treated with DES, histopathological analysis shows evidence of delayed healing due to chronic inflammation, persistent fibrin deposition, and a greater number of uncovered struts in patients with STEMI when compared with stable coronary artery disease.[9] Optical Coherence Tomography in patients with STEMI also suggests an increased risk of uncovered and malapposed struts in lesions treated with DES when compared with BMS.[10]

Chronic inflammation and uncovered struts may become particularly important after cessation of dual antiplatelet therapy (DAPT) 6 to 12 months after stent implantation, which may cause the risks and benefits of DES vis-à-vis BMS to vary over time.[11] Previous meta-analyses investigating clinical outcomes of DES vs. BMS in STEMI patients were limited to a maximum follow-up of 2 years,[4] were restricted to one type of early generation DES,[12,13] or did not examine differences in relative risks of events over time.[4,8] We therefore set out to investigate the long-term safety and effectiveness of early generation DES approved by the US Food and Drug Administration compared with BMS and to determine whether relative risks and benefits of DES vs. BMS varied over time.

# Methods

## Search strategy and selection criteria

We searched Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) (Supplementary material online, *Appendix S1*), and relevant websites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com www.theheart.org) (from the inception of each database to April 2011), checked conference proceedings, relevant reviews, editorials, and meta-analyses and reference lists of identified reports for randomized or quasi-randomized trials in any language that compared sirolimus eluting stents (SES, Cypher or Cypher Select, Cordis, Miami Lakes, FL, USA), or paclitaxel eluting stents (PES, Taxus or Taxus Express, Boston Scientific, Natick, MA, USA) with BMS in adults with STEMI. Two of the authors (T.P. and G.G.S.) performed screening of titles and abstracts, reviewed full-text articles, and determined their eligibility in duplicate.

## Data collection and quality assessment

We extracted characteristics of trials, patients, and interventions, including study design, length of follow-up, components of methodological quality, and source of funding, gender, diabetes status, and smoking status of included patients, stent type, reference vessel diameter, number of stents implanted, length and diameter of the implanted stents, and the recommended duration of DAPT according to the protocol. As components of methodological quality,[14,15] we assessed concealment of allocation, blinding of investigators adjudicating clinical events, and the inclusion of all randomized individuals in the analysis according to the intention-to-treat principle. Concealment of allocation was considered adequate if the investigators responsible for the selection of patients did not know before allocation which treatment was next in line (central randomization, sealed, opaque, sequentially numbered assignment envelopes, etc.). Any procedures based on predictable generation of allocation sequences, and potentially transparent attempts to conceal allocation, such as assignment envelopes which were not opaque or not sealed,[16] were considered inadequate. The analysis was considered to be according to the intention-to-treat principle if all randomized patients were analysed in the group they were originally allocated to, regardless of the treatment actually received. All data were extracted by one reviewer (K.H.) and subsequently checked by a second reviewer (B.K. or B.d.C.).

## Outcomes

We pre-specified definite ST as the primary safety outcome and target vessel revascularization (TVR) as the primary effectiveness outcome. Definite ST was defined as a thrombosis within the stented segment, confirmed by angiography or pathology in accordance with the criteria of the Academic Research Consortium.[17] Target vessel revascularization was defined as repeat percutaneous intervention or bypass surgery of the target vessel done for restenosis or other complications. Data on TVR were unavailable in two trials,[18,19] and we used data on target lesion revascularization as a proxy measure, which was available for one of the trials.[18] We pre-specified the following secondary safety outcomes: cardiac death, defined as any death due to a cardiac cause (for example, myocardial infarction, low output failure, fatal arrhythmia), procedure-related deaths, deaths related to concomitant treatment, and death of unknown cause; myocardial infarction, including fatal and non-fatal non-Q wave or Q wave myocardial infarction; a composite of death or myocardial infarction. Data on the composite of death or myocardial infarction were unavailable in eight trials,[18–25] and we used data on the composite of cardiac death or myocardial infarction as a proxy measure, which was available in two trials.[18,19] The numbers of patients experiencing an event and the overall number of patients at risk were recorded separately for year 1 and subsequent years. For two trials,[26,27] we obtained additional outcome data for the follow-up period beyond 1 year. Outcomes data were extracted by one of the authors (L.R.) and checked by another author (K.H.).

## Statistical analysis

We calculated risk ratios (RR) as measures of treatment effect and used a DerSimonian and Laird random effects model to combine estimates across trials.[28] Two three-arm trials had allocated patients to SES, PES, or BMS and we combined data of SES and PES groups to derive RRs. First, we performed overall analyses using the maximum follow-up duration available for each trial. Then, we performed analyses separately for the first year and for subsequent years accompanied by tests for interaction between RR and time period from random-effects meta-regression. We determined heterogeneity across trials using the $I^2$ statistic and constructed funnel plots (see Web Supplementary material online, *Appendix S2* for details of statistical analysis). Then, we performed analyses stratified by the following characteristics: adequate concealment of allocation, blind adjudication of events, adequacy of analyses in accordance with the intention-to-treat principle, trial size, industry-independent funding, protocol-mandated duration of DAPT, and type of DES. We derived numbers-needed-to-treat (NNTs) and numbers needed-to-harm (NNHs) to prevent or cause one additional event per year when compared with BMS from baseline event rates in BMS arms and the pooled RR comparing DES and BMS.[29] Assumptions for baseline event rates were based on median annual event rates in year 1 and in subsequent years found in BMS arms of included trials and registry studies[7,30–34] comparing first generation DES with BMS in patients with STEMI with at least 300 patients in the BMS group (Supplementary material online, *Appendix S3*). Numbers-needed-to-treat and NNHs were calculated separately for year 1, for years 2–5, and for the entire period of 1–5 years. All analyses were performed using STATA 11.2.

**Table I** Clinical characteristics of trials

| Trial acronym | Stent type | No. of patients | Age, mean (SD) | Males, *n* (%) | Diabetes, *n* (%) | Hypertension, *n* (%) | Smokers, *n* (%) | MVD, *n* (%) | RVD, mean (SD) | No. of stents, mean (SD) | Stent length, mean (SD) | Stent diameter, mean (SD) | Longest FUP, years |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pasceri *et al.* | SES/BMS | 32/33 | 62 (–) | – | – | – | – | – | – | – | – | – | 3 |
| PASSION | PES/BMS | 310/309 | 61 (13) | 470 (76) | 68 (11) | 193 (31) | 319 (52)[a] | 278 (45) | 3.2 (0.5) | 1.3 (0.6) | 19 (6) | 3.2 (0.3) | 5 |
| STRATEGY | SES/BMS | 87/88 | 63 (12)[b] | 128 (73) | 26 (15) | 92 (53) | 70 (40) | 72 (41) | 2.3 (0.5)[b] | – | – | – | 5 |
| BASKET-AMI | SES/PES/BMS | 75/67/74 | – | – | – | – | – | – | – | – | – | – | 3 |
| TYPHOON | SES/BMS | 356/359 | 59 (12) | 558 (78) | 116 (16) | 289 (41) | 356 (50) | 336 (47) | 2.8 (0.6) | 1.1 (0.4) | 21 (8) | 3.1 (0.4) | 4 |
| PASEO | SES/PES/BMS | 90/90/90 | 62 (16) | 190 (70) | 69 (26) | 71 (26) | 68 (25) | – | 3.2 (0.5) | 1.2 (0.5) | 21 (7) | 3.1 (0.4) | 6 |
| SESAMI | SES/BMS | 160/160 | 63 (12) | 256 (80) | 65 (20) | 185 (58) | 174 (54) | 150 (47) | – | 1 (–) | 18 (4) | 3.1 (0.2) | 3 |
| MISSION | SES/BMS | 158/152 | 59 (11) | 241 (78) | 30 (10) | 87 (28) | 169 (55) | 106 (34) | 2.8 (0.6) | – | 26 (12) | 3.3 (0.3) | 3 |
| HAAMU-STENT | PES/BMS | 82/82 | 63 (13) | 118 (72) | 24 (15) | 75 (46) | 70 (43) | – | – | – | – | – | 1 |
| Dìaz de la Llera | SES/BMS | 60/60 | 65 (13) | 95 (79) | 33 (28) | – | 82 (68) | 56 (47) | – | – | 30 (15) | 3.2 (0.4) | 1 |
| MULTI-STRATEGY | SES/BMS | 373/372 | 64 (12) | 565 (76) | 108 (15) | 426 (57) | 277 (37) | 399 (53) | 2.8 (0.4)[b] | 1 (0) | 22 (5) | 3.1 (0.4) | 3 |
| SELECTION | PES/BMS | 40/40 | 61 (–) | 66 (83) | 10 (13) | 37 (46) | 43 (54) | 36 (45) | 2.9 (0.4) | – | 20 (5) | 3.1 (0.3) | 7 mo. |
| GRACIA-3 | PES/BMS | 217/216 | 61 (1) | 358 (83) | 80 (18) | 188 (43) | 210 (48) | 163 (38) | 2.9 (0.04) | – | – | – | 1 |
| HORIZONS-AMI | PES/BMS | 2257/749 | 60 (–)[b] | 2307 (77) | 478 (16) | 1544 (51) | 1429 (48) | – | 2.9 (0.5)[a] | 1.5 (0.8) | 30 (16) | – | 3 |
| DEDICATION | DES/BMS[c] | 313/313 | 62 (–) | 458 (73) | 65 (10) | 207 (33) | 336 (54) | 235 (38) | – | – | 22 (10) | 3.5 (0.5) | 3 |

[a]Includes all patients with a history of smoking, not just current smokers.
[b]Estimated mean and SD from median and IQR.
[c]DEDICATION compares different types of DES without differentiating between SES and PES.
FUP, follow-up; MVD, multivessel disease; RVD, reference vessel diameter; PASSION, paclitaxel-eluting stent vs. conventional stent in myocardial infarction with ST-segment elevation; STRATEGY, Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs. Abciximab and Bare Metal Stent in Myocardial Infarction; BASKET-AMI, Basel Stent Kosten Effektivitäts in Acute Myocardial Infarction Trial; TYPHOON, Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs. Bare Metal Stent in Primary Angioplasty; SESAMI, Sirolimus-Eluting Stent vs. Bare-Metal Stent in Acute Myocardial Infarction; MISSION, A Prospective Randomised Controlled Trial to Evaluate the Efficacy of Drug-Eluting Stents vs. Bare-Metal Stent in Acute Myocardial Infarction Study; HAAMU-STENT, Helsinki Area Acute Myocardial infarction treatment reevalUation—should the patient get a drug-Eluting or a Normal sTent; MULTI-STRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs. Abciximab with Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Versus Conventional Stent in Acute Myocardial Infarction; GRACIA-3, Grupo de Anàlisis de la Cardiopatìa Isquémica Aguda; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Segment-Elevation Myocardial Infarction.

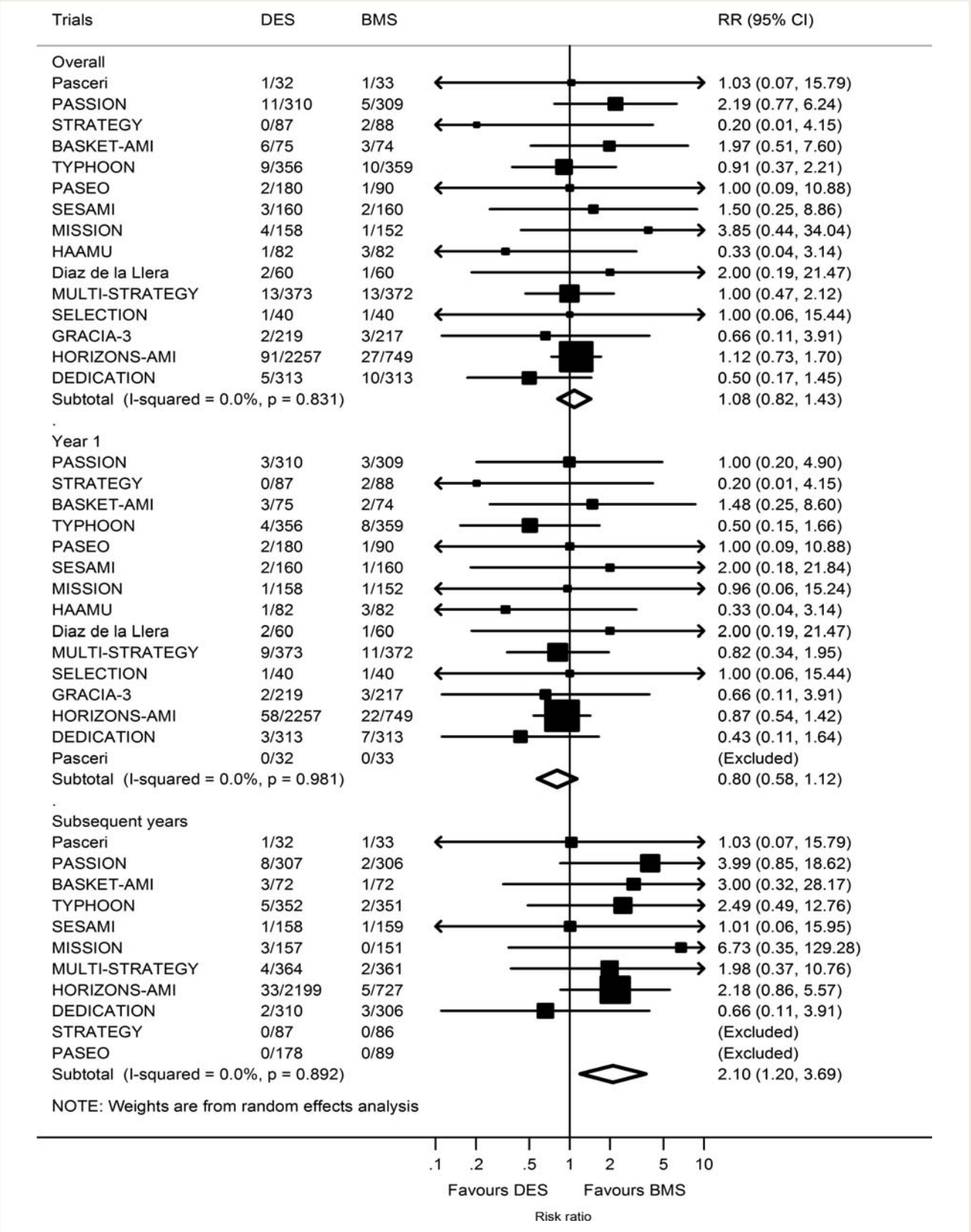


**Figure 1** Number of patients experiencing definite ST out of the total patients DES and BMS. Risk ratios with 95% CI for definite stent thrombosis comparing DES vs. BMS for individual trials and the pooled trials. DES, drug-eluting stent; BMS, bare-metal stent; ST, stent thrombosis.

# Results

We identified 558 references in our literature search and considered 43 to be potentially eligible (Supplementary material online, *Appendix S2*). Forty reports describing 15 trials met our inclusion criteria and were included in the meta-analysis,[18–27,35–59] 13 published as full-text journal articles, and 2 presented at scientific meetings only. The trials had randomly allocated 7867 patients undergoing primary PCI in the setting of STEMI to treatment with either early generation DES or BMS. Seven trials allocated patients to SES,[20,21,23,24,26,27,35] and five to PES.[18,19,22,37,38] Three trials used both types of DES,[25,39,44] two had three arms,[39,44] and one had two arms, with the implantation of SES (47%), PES (40%), or Zotarolimus-eluting stents (13%) in patients in the DES arm remaining at the discretion of the treating physician.[25]

The methodological characteristics of trials are summarized in Supplementary material online, *Appendix S5*. All trials were described as randomized. Concealment of allocation was adequate in four trials.[19,24,25,37] Blind adjudication of events was described in eight trials;[18,19,21,26,27,37,39,44] in one trial,[23] a clinical events committee was described to adjudicate events, but it remained unclear whether members of the committee were aware of the assigned stent type. Seven trials had analysed their data according to the intention-to-treat principle.[18,20,25,27,37,38,44] The maximum length of follow-up ranged from 7 months to 6 years with a duration of follow-up of 3 years or more in 11 trials.[18–21,23–27,37,39,44] Three trials reported funding to be completely independent from industry.[18,19,27] The clinical characteristics of included patients are summarized in *Table 1*. The mean age ranged from 59 to 65 years, the percentage of males from 70 to 83%, the percentage of patients with diabetes from 10 to 28%, and the percentage of patients with multi-vessel disease from 34 to 53%. A loading dose of clopidogrel 300 mg was administered in nine trials[18,19,23,24,26,27,38,39,44] and 300–600 mg in four trials,[21,25,35,37] whereas two trials did not report the loading dose.[20,56] The duration of DAPT recommended according to protocol for patients with DES ranged from 3 to 12 months, with identical recommended durations in DES and BMS patients in all but one trial.[35] Glycoprotein IIb/IIIa inhibitors were administered in >95% of the patients in 11 out of 15 trials,[19–21,24–27,35,37,38,44] in 71 and 74% of the patients in two trials use;[18,23] two other trials did not report the rate of GpIIb/IIIa inhibitor use[39,56] (Supplementary material online, *Appendix S3*). The use of mechanical thrombo-aspiration was not reported, with the exception of one trial (4% of patients),[44] whereas a filterwire was reported in another trial (41% of the patients).[54] Angiographic follow-up was performed in six trials, in 24–95% of the patients.[19–21,23,37,38]

All 15 trials contributed to the analysis of the primary safety endpoint of definite ST, which was reported in 151 patients treated with DES (3.2%) and 83 patients allocated to BMS (2.7%). Nine trials reported ST based on ARC definitions.[19,23–26,37–39,44] *Figure 1* (top) presents the Forest plot with RRs of individual trials scattered around the null effect line at 1, a pooled RR of 1.08 (95% CI 0.82–1.43) and no evidence for heterogeneity between trials ($I^2 = 0\%$,

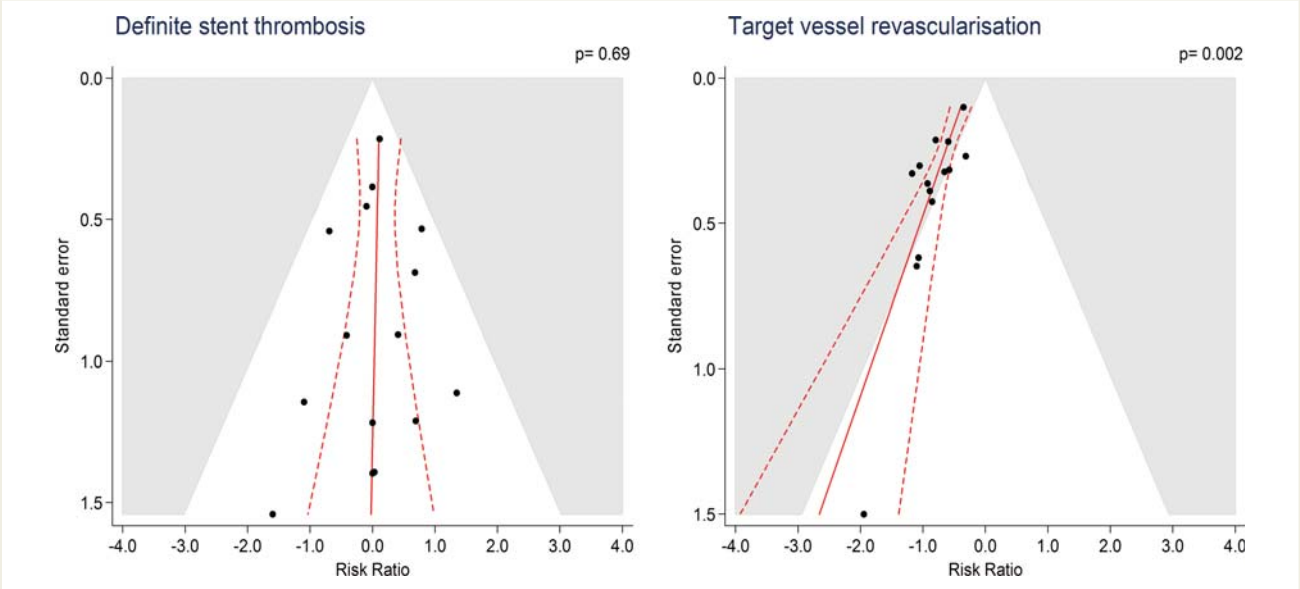


**Figure 2** Contour enhanced funnel plots for definite ST and TVR with log of the RR of individual trials on the *x*-axis scattered against the corresponding standard error on the *y*-axis. The larger a trial, the more events accumulated, the smaller the standard error as a measure of statistical precision. In the absence of bias, the scatter of trials should have the shape of an inverted funnel, with large trials scattering little at the top and small trials scattering considerably at the bottom. If the funnel plot is asymmetrical, this suggests the presence of small study effects, suggesting that methodological problems, selective reporting of outcomes in small trials, and publication bias may have resulted in an overestimation of effects. Red solid lines are prediction lines from univariable meta-regression models with standard error as explanatory variable and red broken lines are corresponding 95% prediction intervals. The more the prediction line deviates from the vertical line, the more pronounced is asymmetry. Contours distinguish between grey areas of significance at a two-sided $P \leq 0.05$ and white areas of non-significance at a two-sided $P > 0.05$. If trials seem to be missing in areas of non-significance, this adds to the notion of the presence of bias. The prediction lines should be interpreted independently of contours. *P*-values are from the Harbord test. ST, stent thrombosis; TVR, target vessel revascularization.

**Table 2 Stratified analysis by characteristics of trials and stent type for overall follow up**

| | Definite stent thrombosis | | | | | Target vessel revascularization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of trials | No. of patients | DES vs. BMS | $I^2$ | *P*-inter | No. of trials | No. of patients | DES vs. BMS | $I^2$ | *P*-inter |
| All trials | 15 | 7867 | 1.08 (0.82–1.43) | 0 | | 14 | 7431 | 0.51 (0.43–0.61) | 24 | |
| Adequate concealment of allocation | | | | | 0.56 | | | | | 0.18 |
| Yes | 4 | 4388 | 1.00 (0.69–1.46) | 0 | | 3 | 3952 | 0.58 (0.43–0.80) | 50 | |
| No/unclear | 11 | 3479 | 1.19 (0.78–1.82) | 0 | | 11 | 3479 | 0.47 (0.38–0.57) | 0 | |
| Blind adjudication of events | | | | | 0.71 | | | | | 0.85 |
| Yes | 9 | 6403 | 1.11 (0.81–1.51) | 0 | | 8 | 5967 | 0.50 (0.39–0.65) | 51 | |
| No/unclear | 6 | 1464 | 0.96 (0.49–1.88) | 0 | | 6 | 1464 | 0.48 (0.36–0.65) | 0 | |
| Intention to treat analysis | | | | | 0.95 | | | | | 0.59 |
| Yes | 7 | 4841 | 1.07 (0.75–1.53) | 0 | | 7 | 4841 | 0.51 (0.38–0.67) | 50 | |
| No/unclear | 8 | 3026 | 1.09 (0.69–1.73) | 0 | | 7 | 2590 | 0.48 (0.37–0.62) | 0 | |
| Trial size | | | | | 0.99 | | | | | 0.043 |
| >300 | 8 | 6777 | 1.08 (0.80–1.46) | 0 | | 7 | 6341 | 0.57 (0.47–0.70) | 29 | |
| <300 | 7 | 1090 | 1.08 (0.47–2.45) | 0 | | 7 | 1090 | 0.36 (0.26–0.51) | 0 | |
| Funding independent from industry | | | | | 0.59 | | | | | 0.58 |
| Yes | 3 | 1230 | 1.09 (0.33–3.66) | 33 | | 2 | 794 | 0.56 (0.31–1.02) | 46 | |
| No/unclear | 12 | 6637 | 1.05 (0.78–1.41) | 0 | | 12 | 6637 | 0.50 (0.41–0.60) | 28 | |
| Type of stent | | | | | 0.99 | | | | | 0.10 |
| SES | 9 | 1391 | 1.14 (0.72–1.81) | 0 | | 8 | 1035 | 0.45 (0.34–0.59) | 0 | |
| PES | 6 | 2998 | 1.15 (0.79–1.66) | 0 | | 6 | 2779 | 0.58 (0.43–0.79) | 32 | |
| Protocol mandated duration of DAPT | | | | | 0.40 | | | | | 0.58 |
| 9 or 12 months | 7 | 2056 | 0.83 (0.42–1.61) | 0 | | 6 | 1620 | 0.47 (0.35–0.61) | 0 | |
| 3 or 6 months | 8 | 5811 | 1.14 (0.84–1.56) | 0 | | 8 | 5811 | 0.51 (0.39–0.66) | 47 | |

Note that one two-arm trial did not contribute to the analysis according to stent type since different stent types were used in the DES arm, and two three-arm trials allowed both a comparison of SES with BMS and a comparison of PES with BMS. Therefore, 16 comparisons are reported in stratified analysis according to stent type. *P*-inter, *P* for interaction between subgroups using meta regression.

*P* for heterogeneity = 0.83). *Figure 2* (left) presents the corresponding funnel plot. The scatter of effect estimates and the prediction line from meta-regression models with standard error as an explanatory variable indicated complete symmetry, with all trials in white areas of non-significance at $P > 0.05$. The regression test was negative ($P = 0.69$). Stratified analyses according to the methodological and clinical characteristics of trials (*Table 2*, left) showed only minor variation across strata and corresponding tests for interaction were negative. *Figure 1* shows forest plots of definite ST occurring during the first year (middle) and subsequent years (bottom). During the first year after stent implantation, patients with DES tended to be less likely than patients with BMS to experience definite ST (RR 0.80, 95% CI 0.58–1.12). Conversely, patients with DES were more likely than patients with BMS to experience definite ST during subsequent years (RR 2.10, 95% CI 1.20–3.69), and a test of interaction between RR of definite ST and time was positive (*P* for interaction = 0.009). Results were similar for the composite of definite or probable ST; definite or probable ST during the first year tended to be less likely in patients with DES than with BMS (RR 0.81, 95% CI 0.60–1.11), whereas the risk during subsequent years was greater (RR 2.01, 95% CI 0.79–1.31), with a positive test for interaction (*P* for interaction = 0.015).

Fourteen trials contributed to the analysis of the primary efficacy endpoint TVR, which was performed in 429 patients treated with DES (9.0%) and 452 patients treated with BMS (14.6%), with a pooled RR of 0.51 (95% CI 0.43–0.61, *Figure 3*, top) and no evidence for heterogeneity between trials ($I^2 = 24\%$, *P* for heterogeneity = 0.19). *Figure 2* (right) presents the corresponding funnel plot. The scatter of effect estimates and the prediction line from meta-regression models with standard error as an explanatory variable indicated asymmetry and the contours to distinguish between areas of significance and non-significance at $P = 0.05$ suggested missing trials in the white area of non-significance. The regression test for asymmetry was positive at $P = 0.002$. Accordingly, stratified analyses according to the methodological and clinical characteristics indicated a greater benefit from DES in small when compared with large trials (*Table 2*, right). In the analysis stratified according to the time (*Figure 3*, middle and bottom), we found a more pronounced reduction in the relative risk of TVR for DES when compared

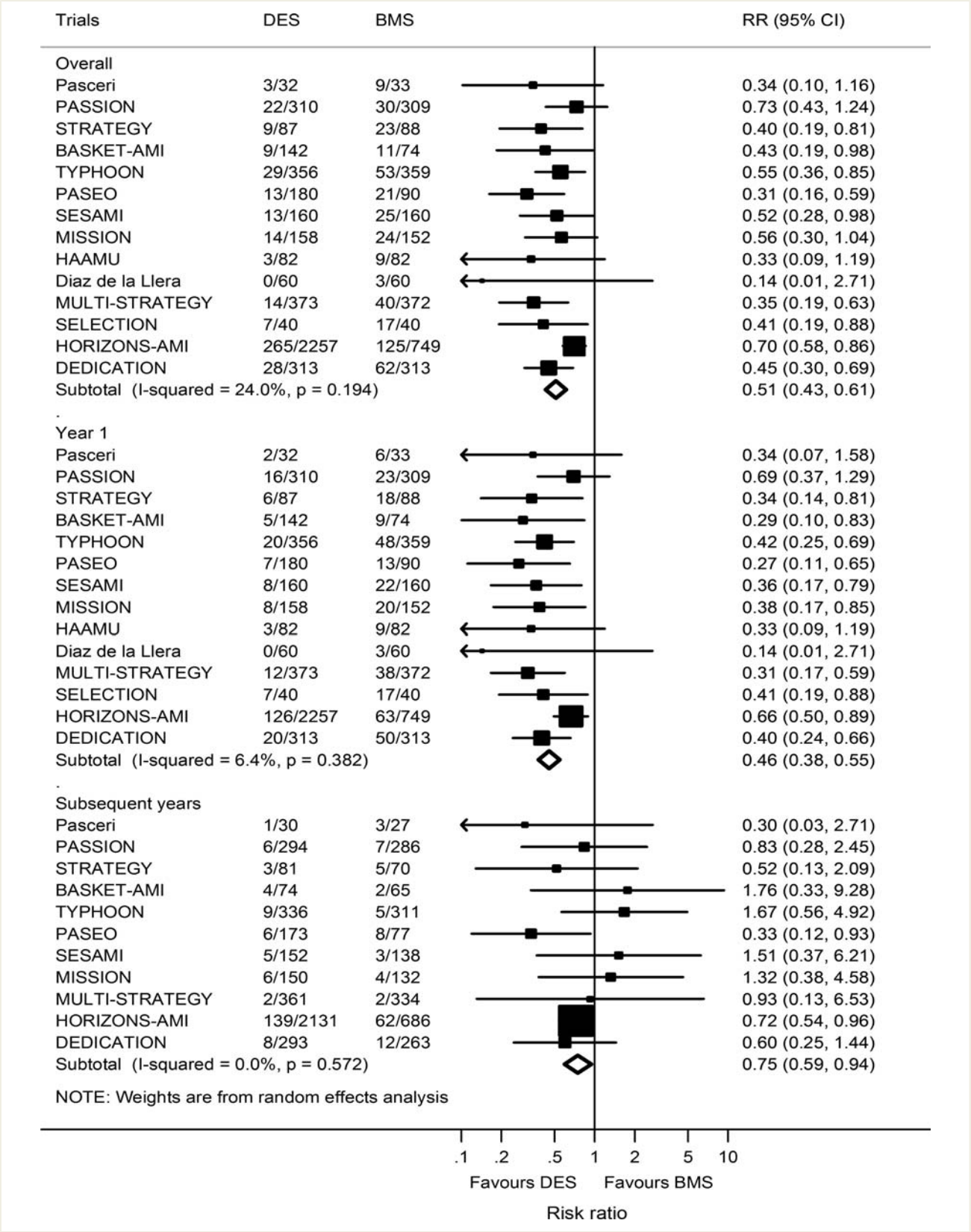


**Figure 3** Number of patients requiring TVR among all total patients in DES and BMS. Risk ratios for definite stent thrombosis comparing DES vs. BMS for individual trials and the pooled population. DES, drug-eluting stent; BMS, bare-metal stent; ST, stent thrombosis; TVR, target vessel revascularization.

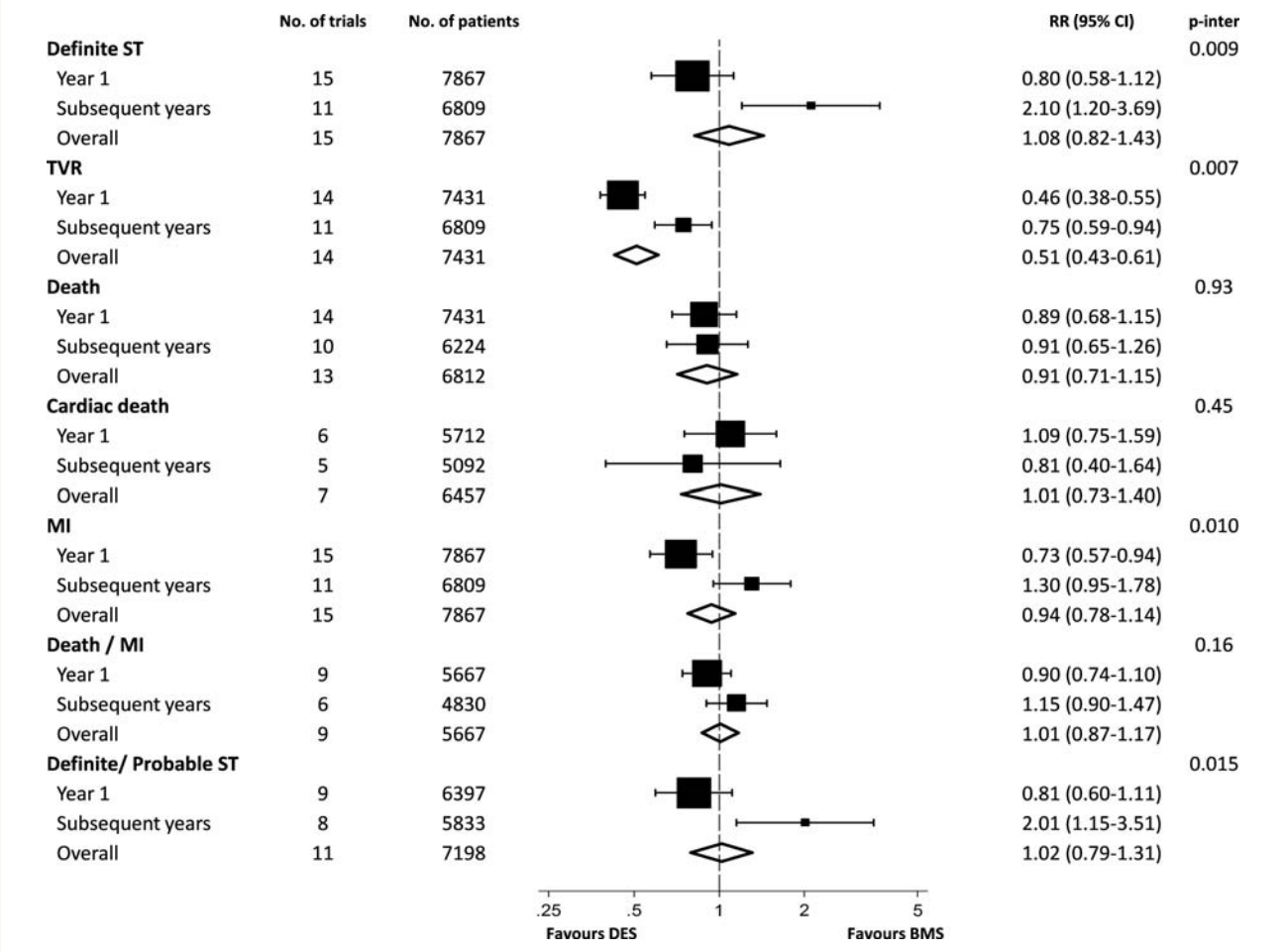


**Figure 4** Risk of clinical outcomes comparing DES with BMS stratified according to time. DES, drug-eluting stent; BMS, bare-metal stent. *P*-inter: *P* for interaction between year 1 and subsequent years using meta-regression.

with BMS during the first year (RR 0.46, 95% CI 0.38–0.55) as opposed to subsequent years (RR 0.75, 95% CI 0.59–0.94), with a positive test of interaction between RR of TVR and time (*P* for interaction = 0.007, *Figure 4*, top).

Sensitivity analyses of time-dependent effects after restriction to trials of higher methodological quality showed similar results as the main analysis for both primary endpoints (*Table 3*). Stratified analyses according to the stent type also suggested similar results for definite ST, but more pronounced time-dependent effects for TVR with SES than with PES, even though confidence intervals were wide and overlapping (*Table 3*). A *post hoc* analysis of time-dependent effects after exclusion of the largest trial, HORIZONS-AMI,[37] yielded again similar results. For definite ST, the RR was 0.75 during the first year (95% CI 0.47–1.18) and 2.06 during subsequent years (95% CI 1.02–4.15; *P* for interaction = 0.028). For TVR, the RR was 0.39 during the first year (95% CI 0.32–0.48) and 0.80 during subsequent years (95% CI 0.54–1.19; *P* for interaction = 0.005).

*Figure 4* presents full analyses of primary and secondary outcomes overall and stratified according to the time period. We found variation across time periods for definite ST, TVR, MI, and the composite of definite or probable ST, all with positive tests for interaction between treatment effect and time (*P* for interaction $\leq$0.015). For remaining outcomes, there was no evidence to suggest time-dependent effects. *Table 4* presents estimated NNTs to prevent one event and NNHs to cause one event during the first year and subsequent years and for the entire duration of follow-up for all outcomes. The NNT to prevent one definite ST compared with BMS during the first year was 238, but the estimate did not reach conventional levels of statistical significance ($P = 0.17$) and the 95% CI included infinity (95% CI 114 to $\infty$). The NNH to cause one additional definite ST during the subsequent 4 years was 76 (95% CI 31–417, $P = 0.009$). Taken together, this resulted in a NNH to cause one additional definite ST over 5 years of 111, with the 95% CI, including infinity (95% CI 21 to $\infty$, $P = 0.46$). Numbers-needed-to-treat of 19 were reached to avoid one TVR during the first year (95% CI 16–23), 71 during the subsequent 4 years (95% CI 44–298), and 15 for years 1–5 combined (95% CI 11–27), with all estimates reaching conventional levels of statistical significance ($P \leq 0.015$). Additional statistical trends were only observed for MI, with a NNT of 79 to prevent one MI during the first year (95% CI 49–355, $P = 0.01$) and a NNH of 76 to cause

**Table 3 Sensitivity analysis of time-dependent effects after restriction of trials of higher methodological quality and after stratification according to stent type**

| | Definite stent thrombosis | | | | | Target vessel revascularization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of trials | No. of patients | DES vs. BMS | $I^2$ | *P*-inter | No. of trials | No. of patients | DES vs. BMS | $I^2$ | *P* inter |
| All trials | | | | | 0.009 | | | | | 0.007 |
| Year 1 | 15 | 7867 | 0.80 (0.58–1.12) | 0 | | 14 | 7431 | 0.46 (0.38–0.55) | 6 | |
| Subsequent years | 11 | 7067 | 2.10 (1.20–3.69) | 0 | | 11 | 7067 | 0.75 (0.59–0.94) | 0 | |
| Trials with concealed allocation | | | | | 0.20 | | | | | 0.26 |
| Year 1 | 4 | 4388 | 0.82 (0.53–1.27) | 0 | | 3 | 7904 | 0.50 (0.33–0.76) | 54 | |
| Subsequent years | 3 | 3952 | 1.61 (0.73–3.57) | 0 | | 3 | 7904 | 0.73 (0.56–0.95) | 0 | |
| Trials with blind adjudication | | | | | 0.019 | | | | | 0.063 |
| Year 1 | 9 | 6403 | 0.82 (0.57–1.18) | 0 | | 8 | 5967 | 0.44 (0.33–0.59) | 40 | |
| Subsequent years | 8 | 5967 | 2.21 (1.18–4.14) | 0 | | 8 | 5967 | 0.71 (0.56–0.91) | 0 | |
| Trials with ITT analysis | | | | | 0.068 | | | | | 0.30 |
| Year 1 | 7 | 4841 | 0.81 (0.53–1.23) | 0 | | 7 | 4841 | 0.49 (0.37–0.65) | 28 | |
| Subsequent years | 6 | 4761 | 1.95 (0.96–3.95) | 0 | | 6 | 4761 | 0.67 (0.52–0.86) | 0 | |
| Large trials | | | | | 0.016 | | | | | 0.022 |
| Year 1 | 8 | 6777 | 0.79 (0.56–1.14) | 0 | | 7 | 6341 | 0.48 (0.37–0.61) | 34 | |
| Subsequent years | 7 | 6341 | 2.12 (1.17–3.84) | 0 | | 7 | 6341 | 0.79 (0.62–1.01) | 0 | |
| Trials with industry independent funding | | | | | 0.21 | | | | | 0.67 |
| Year 1 | 3 | 1230 | 0.69 (0.23–2.07) | 0 | | 2 | 794 | 0.52 (0.26–1.04) | 43 | |
| Subsequent years | 2 | 794 | 3.99 (0.85–18.6) | 0 | | 2 | 794 | 0.70 (0.30–1.64) | 0 | |
| SES | | | | | 0.096 | | | | | 0.027 |
| Year 1 | 9 | 2779 | 0.83 (0.47–1.47) | 0 | | 8 | 2064 | 0.35 (0.25–0.48) | 0 | |
| Subsequent years | 8 | 2567 | 2.18 (0.91–5.23) | 0 | | 7 | 1868 | 0.80 (0.45–1.42) | 0 | |
| PES | | | | | 0.053 | | | | | 0.42 |
| Year 1 | 6 | 4485 | 0.84 (0.55–1.30) | 0 | | 6 | 4408 | 0.60 (0.47–0.76) | 0 | |
| Subsequent years | 3 | 3657 | 2.57 (1.15–5.72) | 0 | | 4 | 4008 | 0.70 (0.54–0.92) | 0 | |

*P*-inter, *P* for interaction between year 1 and subsequent years using meta regression.

one MI compared with BMS during the subsequent 4 years (95% CI 29 to ∞, $P = 0.10$). Taken together, this resulted in a clinically irrelevant NNH of 1961 to cause one MI during years 1–5 (95% CI 22 to ∞, $P = 0.98$).

# Discussion

This meta-analysis of 15 randomized trials in 7867 patients who underwent primary PCI for STEMI suggests time-dependent clinical effects of early generation FDA-approved DES compared with BMS for definite ST, definite or probable ST, TVR, and myocardial infarction. During the first year, there was a safety advantage of DES over BMS in terms of lower rates of ST and MI, whereas an opposite pattern emerged during subsequent years, with a safety advantage of BMS over DES. This qualitative interaction between risks and benefits was particularly robust for the endpoint definite ST, with a trend towards a 20% relative risk reduction during the first year, which was offset by a more than 100% relative risk increase during subsequent years ($P$ for interaction = 0.009). For the primary effectiveness outcome of TVR, we did not find a qualitative, but still an important quantitative interaction, with a more than 50% relative risk reduction in TVR during the first year, which decreased but was maintained at 25% during subsequent years ($P$ for interaction = 0.007). Overall, the effectiveness of DES in reducing the rate of TVR was maintained across the entire duration of follow-up, with an estimated NNT to prevent one TVR during the first 5 years after stent implantation of 15, which is clearly clinically relevant. For none of the safety outcomes, we found any evidence for overall risk increases associated with DES, with risk ratios near one for death overall, cardiac death, MI, ST, and the composite of death or MI. Conversely, there was clear evidence of late harm with an increased risk of definite and definite or probable ST as well as MI.

What does this meta-analysis add in comparison with previously published systematic reviews? First, we included 15 studies with a total of 7867 patients. Therefore, this is the largest meta-analysis of

**Table 4** Estimated numbers-needed-to-treat and numbers-needed-to-harm for different outcomes

| | Year 0–1 | | | | Years 1–5 | | | | Years 0–5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rates, % | | NNT/NNH | P-value | Rates, % | | NNT/NNH | P-value | Rates, % | | NNT/NNH | P-value |
| | BMS | DES | | | BMS | DES | | | BMS | DES | | |
| Primary outcomes | | | | | | | | | | | | |
| Definite stent thrombosis | 2.0 | 1.6 | NNT 238 (NNT 114 to ∞) | 0.17 | 1.2 | 2.5 | NNH 76 (NNH 417–31) | 0.009 | 3.2 | 4.1 | NNH 111 (NNH 21 to ∞) | 0.46 |
| Target vessel revascularization | 9.8 | 4.5 | NNT 19 (NNT 16–23) | <0.0001 | 5.6 | 4.2 | NNT 71 (NNT 44–298) | 0.015 | 15.4 | 8.7 | NNT 15 (NNT 11–27) | <0.001 |
| Secondary outcomes | | | | | | | | | | | | |
| Death overall | 7.7 | 6.9 | NNT 118 (NNT 41 to ∞) | 0.38 | 8.0 | 7.3 | NNT 139 (NNT 36 to ∞) | 0.58 | 15.7 | 14.1 | NNT 64 (NNT 16 to ∞) | 0.63 |
| Cardiac death | 3.9 | 4.3 | NNH 285 (NNH 43 to ∞) | 0.65 | 4.0 | 3.2 | NNT 132 (NNT 42 to ∞) | 0.59 | 7.9 | 7.5 | NNT 244 (NNT 22 to ∞) | 0.90 |
| Myocardial infarction | 4.7 | 3.4 | NNT 79 (NNT 49–355) | 0.01 | 4.4 | 5.7 | NNH 76 (NNH 29 to ∞) | 0.10 | 9.1 | 9.2 | NNH 1961 (NNH 22 to ∞) | 0.98 |
| Death or myocardial infarction | 12.4 | 11.2 | NNT 81 (NNT 31 to ∞) | 0.30 | 11.6 | 13.3 | NNH 57 (NNH 18 to ∞) | 0.26 | 24.0 | 24.5 | NNH 200 (NNH 10 to ∞) | 0.90 |
| Definite or probable stent thrombosis | 2.3 | 1.9 | NNT 229 (NNT 109 to ∞) | 0.18 | 1.2 | 2.4 | NNH 80 (NNH 32–521) | 0.014 | 3.5 | 4.3 | NNH 123 (NNH 21 to ∞) | 0.53 |

Data are NNH or NNT (95% confidence interval).
BMS, bare-metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; NNT, number-needed-to-treat to avoid one event over specified time period; NNH, number-needed-to-harm to cause one event over specified time period.

its kind. Secondly, we focused on long-term outcomes, and provide the longest follow-up reported to date with a maximum length of follow-up up to 6 years. This is important as previous large-scale trials and meta-analyses failed to detect differences in late safety outcomes with the use of early generation DES, prematurely concluding the absence of harm among STEMI patients. Thirdly, we examined the data for the presence of small study effects using contour-enhanced funnel plots and regression tests. Finally and most importantly, we systematically analysed time-dependent effects of stent-type allocation on all clinical outcomes (*Figure 4*). Our analysis indicates that the use of early generation DES is associated with a significantly lower risk of TVR and MI as well as a trend towards fewer definite ST during the period of up to 1 year, whereas a reverse pattern of a higher risk of definite ST and a trend towards more MIs becomes apparent during the period beyond 1 year. This suggests that the long-term safety of DES needs further improvement.

Patients with STEMI are at increased risk of ST when compared with patients with stable coronary artery disease both after DES and after BMS implantation.[7,8,60] However, the observed differential in timing of ST suggests differences in the underlying pathophysiological pathways leading to this adverse event after DES implantation. Thus, early ST is closely related to the acute phase after the coronary event and procedure, with pronounced activation of platelets and the coagulation cascade. In this context, experimental data suggest that durable polymer-based DES exert anti-thrombogenic properties resulting in a lower degree of thrombus adhesion,[61] which may be of particular importance among STEMI patients. Along this line, the results of the present study provide preliminary clinical evidence of a somewhat lower risk of definite ST and MI after DES when compared with BMS implantation among STEMI patients. Conversely, ST occurring later in the process may be related to a chronic process with delayed arterial healing and vessel remodelling due to chronic local inflammation potentially related to the persistence of durable polymers[62] and/or long-term effects of eluted drugs. Along this line, autopsy data indicate a differential healing response of DES implanted into plaques of patients with STEMI when compared with stable coronary artery disease with evidence of persistent inflammation and a higher proportion of uncovered struts among coronary segments treated with DES than BMS.[9] Among patients treated with DES, incomplete stent apposition has been recognized as an important morphological substrate associated with the occurrence of very late ST.[63] It is more frequently observed in STEMI patients than in those who undergo DES implantation for stable angina and may be related to incomplete stent apposition at the time of implantation, presence of jailed thrombus with subsequent resolution, or vessel remodelling in response to toxic effects of the drug or polymer. In addition, optical coherence tomography[10] and intravascular ultrasound studies[52] among STEMI patients provide evidence for a higher rate of uncovered stent struts as well as incomplete stent apposition in DES compared with BMS. All these factors may be of particular relevance upon discontinuation of DAPT during long-term follow-up.

The higher risk of definite ST with early generation DES than BMS more than 1 year after stent implantation directly translated into an increased risk of myocardial infarction, with identical

NNHs of 76 to cause one event for both ST and MI. Whether prolongation of DAPT beyond 1 year among patients with STEMI who are at a higher risk of very late ST compared with other patient subsets may overcome this disadvantage, which could in turn translate into a lower overall relative risk of ST and MI, remains subject to debate. In addition, the use of newer generation DES with durable polymers of improved biocompatibility,[64] biodegradable polymers which dissolve completely once the drug is eluted,[11] or even fully bioresorbable vascular scaffolds[65] are currently being investigated to address this issue in STEMI patients.[66,67]

This meta-analysis demonstrated a sustained benefit of DES when compared with BMS in reducing the risk of TVR. The magnitude of the relative risk reduction of approximately 50% was comparable to what was found in randomized trials of patients with stable coronary artery disease and is clinically important with a NNT of only 15.[5] The relative risk reduction in TVR observed during the first year decreased considerably during subsequent years, however ($P$ for interaction = 0.007).[68] The decrease in benefit over time was previously referred to as late catch-up phenomenon[69] and some studies found DES associated with delayed late lumen loss beyond the first year of follow-up.[68,70] Our results suggest that the increased rate in VLST requiring repeat intervention might contribute to this phenomenon. We were also surprised to find evidence of small study effects[71,72] for TVR, suggesting that methodological problems[14] and selective reporting of outcomes[73] in small trials combined with publication bias[74] may have resulted in an overestimation of the effectiveness of first-generation DES.

## Conclusions

The use of early generation DES in primary PCI for STEMI is associated with a large reduction in TVR and a trend towards less definite ST during the first year, which is offset by an increased risk of very late ST and accompanying clinical outcomes during subsequent years.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

# Author contributions

L.R. and S.W. conceived the study. P.J., B.K., L.R., and S.W. wrote the study protocol. B.K. and P.J. did the analysis and interpreted the analysis in collaboration with T.P., L.R., S.W., and all other authors. B.K., K.H., B.R.d.C., L.R., T.P., and G.S. were responsible for the acquisition of data. B.K., T.P., K.H., and P.J. wrote the first draft. All authors critically revised the report for important intellectual content and approved the final version.

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## References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
2. Roubin GS, Cannon AD, Agrawal SK, Macander PJ, Dean LS, Baxley WA, Breland J. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. *Circulation* 1992;**85**:916–927.
3. Schomig A, Kastrati A, Mudra H, Blasini R, Schuhlen H, Klauss V, Richardt G, Neumann FJ. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. *Circulation* 1994;**90**:2716–2724.
4. Brar SS, Leon MB, Stone GW, Mehran R, Moses JW, Brar SK, Dangas G. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. *J Am Coll Cardiol* 2009;**53**:1677–1689.
5. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007;**370**:937–948.
6. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;**369**:667–678.
7. Kukreja N, Onuma Y, Garcia-Garcia H, Daemen J, van Domburg R, Serruys PW. Primary percutaneous coronary intervention for acute myocardial infarction: long-term outcome after bare metal and drug-eluting stent implantation. *Circ Cardiovasc Interv* 2008;**1**:103–110.
8. Brodie B, Pokharel Y, Fleishman N, Bensimhon A, Kissling G, Hansen C, Milks S, Cooper M, McAlhany C, Stuckey T. Very late stent thrombosis after primary percutaneous coronary intervention with bare-metal and drug-eluting stents for ST-segment elevation myocardial infarction: a 15-year single-center experience. *JACC Cardiovasc Interv* 2011;**4**:30–38.
9. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation* 2008;**118**:1138–1145.
10. Guagliumi G, Costa MA, Sirbu V, Musumeci G, Bezerra HG, Suzuki N, Matiashvili A, Lortkipanidze N, Mihalcsik L, Trivisonno A, Valsecchi O, Mintz GS, Dressler O, Parise H, Maehara A, Cristea E, Lansky AJ, Mehran R, Stone GW. Strut coverage and late malapposition with paclitaxel-eluting stents compared with bare metal stents in acute myocardial infarction: optical coherence tomography substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial. *Circulation* 2011;**123**:274–281.
11. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn H, Eerdmans P, van Es G-A, Meier B, Windecker S, Jüni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;**378**:1940–1948.
12. de Luca G, Valgimigli M, Spaulding C, Menichelli M, Brunner-La Rocca HP, van der Hoeven BL, Di Lorenzo E, de la Llera LSD, Pasceri V, Pittl U, Percoco G, Violini R, Stone GW. Short and long-term benefits of sirolimus-eluting stent in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *J Thromb Thrombolysis* 2009;**28**:200–210.
13. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis

of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;**356**:1030–1039.
14. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;**323**:42–46.
15. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**:601–605.
16. Herbison P, Hay-Smith J, Gillespie WJ. Different methods of allocation to groups in randomized trials are associated with different levels of bias. A meta-epidemiological study. *J Clin Epidemiol* 2011;**64**:1070–1075.
17. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys P. Clinical end points in coronary stent trials. A case for standardized definitions. *Circulation* 2007;**115**:2344–2351.
18. Laarman GJ, Suttorp MJ, Dirksen MT, van Heerebeek L, Kiemeneij F, Slagboom T, van der Wieken LR, Tijssen JG, Rensing BJ, Patterson M. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006;**355**:1105–1113.
19. Sanchez PL, Gimeno F, Ancillo P, Sanz JJ, Alonso-Briales JH, Bosa F, Santos I, Sanchis J, Bethencourt A, Lopez-Messa J, De Prado AP, Alonso JJ, San Roman JA, Fernandez-Aviles F. Role of the paclitaxel-eluting stent and tirofiban in patients with st-elevation myocardial infarction undergoing postfibrinolysis angioplasty the GRACIA-3 randomized clinical trial. *Circ Cardiovasc Interv* 2010; **3**:297–307.
20. Pasceri V, Granatelli C, Pristipino C, Pelliccia F, Speciale G, Pironi B, Roncella A, Richichi G. A randomized trial of a Rapamycin-Eluting stent in acute myocardial infarction: preliminary results. *Am J Cardiol* 2003;**92**(Suppl. 6A):1L.
21. van der Hoeven BL, Liem SS, Jukema JW, Suraphakdee N, Putter H, Dijkstra J, Atsma DE, Bootsma M, Zeppenfeld K, Oemrawsingh PV, van der Wall EE, Schalij MJ. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome. Results From the MISSION! Intervention Study. *J Am Coll Cardiol* 2008;**51**:618–626.
22. Tierala I, Syvanne M, Kupari M. Comparison of Paclitaxel-Eluting with Bare Metal Stents in Acute Myocardial Infarction: The HAAMU-STENT study. Presented at the Transcatheter Cardiovascular Therapeutics meeting (TCT 2006), Washington, DC, October 2006. www.cardiosource.com (accessed 7 June 2011).
23. Spaulding C, Henry P, Teiger E, Beatt K, Bramucci E, Carrie D, Slama M, Merkely B, Erglis A, Margheri M, Varenne O, Cebrian A, Stoll HP, Snead D, Bode C. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006;**355**:1093–1104.
24. Menichelli M, Parma A, Pucci E, Fiorilli R, De Felice F, Nazzaro M, Giulivi A, Alborino D, Azzellino A, Violini R. Randomized Trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol* 2007;**49**:1924–1930.
25. Kelbaek H, Thuesen L, Helqvist S, Clemmensen P, Klovgaard L, Kaltoft A, Andersen B, Thuesen H, Engstrom T, Botker HE, Saunamaki K, Krusell LR, Jorgensen E, Hansen HHT, Christiansen EH, Ravkilde J, Kober L, Kofoed KF, Terkelsen CJ, Lassen JF. Drug-eluting versus bare metal stents in patients with ST-segment-elevation myocardial infarction: eight-month follow-up in the drug elution and distal protection in acute myocardial infarction (DEDICATION) trial. *Circulation* 2008;**118**:1155–1162.
26. Valgimigli M, Campo G, Percoco G, Bolognese L, Vassanelli C, Colangelo S, de Cesare N, Rodriguez AE, Ferrario M, Moreno R, Piva T, Sheiban I, Pasquetto G, Prati F, Nazzaro MS, Parrinello G, Ferrari R. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA* 2008;**299**:1788–1799.
27. Valgimigli M, Percoco G, Malagutti P, Campo G, Ferrari F, Barbieri D, Cicchitelli G, McFadden EP, Merlini F, Ansani L, Guardigli G, Bettini A, Parrinello G, Boersma E, Ferrari R. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA* 2005;**293**:2109–2117.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**: 177–188.
29. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses—sometimes informative, usually misleading. *BMJ* 1999;**318**: 1548–1551.
30. Brodie BR, Stuckey T, Downey W, Humphrey A, Nussbaum M, Laurent S, Bradshaw B, Metzger C, Hermiller J, Krainin F, Juk S, Cheek B, Duffy P, Simonton CA. Outcomes with drug-eluting stents versus bare metal stents in acute ST-elevation myocardial infarction: results from the Strategic Transcatheter Evaluation of New Therapies (STENT) Group. *Catheter Cardiovasc Interv* 2008;**72**: 893–900.
31. Mauri L, Silbaugh TS, Garg P, Wolf RE, Zelevinsky K, Lovett A, Varma MR, Zhou Z, Normand SL. Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med* 2008;**359**:1330–1342.
32. Nakamura S, Bae J-H, Cahyadi Y, Udayachalerm W, Tresukosol D, Tansuphaswadikul S. Three-year follow-up patients with ST-segment elevation acute myocardial infarction treated with sirolimus-eluting stent and paclitaxel-eluting stent: multicenter registry in Asia. *Circulation* 2006;**114**:II_516.
33. Vlaar PJ, Rihal CS, Singh M, Lennon R, Ting HH, Bresnahan JF, Holmes DR Jr. Safety and efficacy of drug-eluting stent for ST-segment elevation myocardial infarction in an unselected consecutive cohort. *Catheter Cardiovasc Interv* 2008;**71**: 764–769.
34. Jensen LO, Tilsted HH, Thayssen P, Kaltoft A, Maeng M, Lassen JF, Hansen KN, Madsen M, Ravkilde J, Johnsen SP, Sorensen HT, Thuesen L. Paclitaxel and sirolimus eluting stents versus bare metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. *EuroIntervention* 2010;**5**:898–905.
35. Diaz de la Llera LS, Ballesteros S, Nevado J, Fernandez M, Villa M, Sanchez A, Retegui G, Garcia D, Martinez A. Sirolimus-eluting stents compared with standard stents in the treatment of patient with primary angioplasty. *Am Heart J* 2007;**154**: 164.e1–164.e6.
36. Valgimigli M, Campo G, Arcozzi C, Malagutti P, Carletti R, Ferrari F, Barbieri D, Parrinello G, Percoco G, Ferrari R. Two-year clinical follow-up after sirolimus-eluting versus bare-metal stent implantation assisted by systematic glycoprotein IIb/IIIa inhibitor infusion in patients with myocardial infarction. *J Am Coll Cardiol* 2007;**50**:138–145.
37. Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Mockel M, Ochala A, Kellock A, Parise H, Mehran R. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 2009;**360**:1946–1959.
38. Chechi T, Vittori G, Biondi Zoccai GGL, Vecchio S, Falchetti E, Spaziani G, Baldereschi G, Giglioli C, Valente S, Margheri M. Single-center randomized evaluation of paclitaxel-eluting versus conventional stent in acute myocardial infarction (SELECTION). *J Interv Cardiol* 2007;**20**:282–291.
39. Leibundgut G, Nietlispach F, Pittl U, Brunner-La Rocca H, Kaiser CA, Pfisterer ME. Stent thrombosis up to 3 years after stenting for ST-segment elevation myocardial infarction versus for stable angina—comparison of the effects of drug-eluting versus bare-metal stents. *Am Heart J* 2009;**158**:271–276.
40. Dirksen MT, Vink MA, Suttorp MJ, Tijssen JG, Patterson MS, Slagboom T, Kiemeneij F, Laarman GJ, Paclitaxel-Eluting Stent versus Conventional S, in Myocardial Infarction with STSEi. Two year follow-up after primary PCI with a paclitaxel-eluting stent versus a bare-metal stent for acute ST-elevation myocardial infarction (the PASSION trial): a follow-up study. *EuroIntervention* 2008;**4**: 64–70.
41. Vink MA, Dirksen MT, Suttorp MJ, Tijssen JGP, Van Etten J, Patterson MS, Slagboom T, Kiemeneij F, Laarman GJ. 5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2011;**4**:24–29.
42. Tebaldi M, Arcozzi C, Campo G, Percoco G, Ferrari R, Valgimigli M, Investigators S, Tebaldi M, Arcozzi C, Campo G, Percoco G, Ferrari R, Valgimigli M. The 5-year clinical outcomes after a randomized comparison of sirolimus-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2009;**54**:1900–1901.
43. Spaulding C, Teiger E, Commeau P, Varenne O, Bramucci E, Slama M, Beatt K, Tirouvanziam A, Polonski L, Stella PR, Clugston R, Fajadet J, De Boisgelin X, Bode C, Carri D, Erglis A, Merkely B, Hosten S, Cebrian A, Wang P, Stoll HP, Henry P. Four-year follow-up of TYPHOON (Trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). *JACC Cardiovasc Interv* 2011;**4**:14–23.
44. Di Lorenzo E, De Luca G, Sauro R, Varricchio A, Capasso M, Lanzillo T, Manganelli F, Mariello C, Siano F, Pagliuca MR, Stanco G, Rosato G. The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) Randomized Trial. *JACC Cardiovasc Interv* 2009;**2**:515–523.
45. Di Lorenzo E, Sauro R, Varricchio A, Capasso M, Lanzillo T, Manganelli F, Mariello C, Siano F, Pagliuca MR, Stanco G, Rosato G, De Luca G. Benefits of drug-eluting stents as compared to bare metal stent in ST-segment elevation myocardial infarction: four year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angiOplasty (PASEO) randomized trial. *Am Heart J* 2009;**158**:e43–e50.
46. Di Lorenzo E, Sauro R, Varricchio A, Carbone G, Cortese G, Capasso M, Lanzillo T, Manganelli F, Mariello C, Siano F, Pagliuca MR, Stanco G, Rosato G, De Luca G. Long-Term outcome of drug-eluting stents compared with bare metal stents in ST-segment elevation myocardial infarction: results of the paclitaxel- or sirolimus-eluting stent versus bare metal stent in Primary Angioplasty (PASEO) Randomized Trial. *Circulation* 2009;**120**:964–972.

47. Violini R, Musto C, De Felice F, Nazzaro MS, Cifarelli A, Petitti T, Fiorilli R. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (sirolimus-eluting stent versus bare-metal stent in acute myocardial infarction) trial. *J Am Coll Cardiol* 2010;**55**:810–814.
48. Atary JZ, Bergheanu SC, van der Hoeven BL, Atsma DE, Bootsma M, van der Kley F, Zeppenfeld K, Jukema JW, Schalij MJ, Atary JZ, Bergheanu SC, van der Hoeven BL, Atsma DE, Bootsma M, van der Kley F, Zeppenfeld K, Jukema JW, Schalij MJ. Impact of sirolimus-eluting stent implantation compared to bare-metal stent implantation for acute myocardial infarction on coronary plaque composition at nine months follow-up: a Virtual Histology intravascular ultrasound analysis. Results from the Leiden MISSION! Intervention Study. *EuroIntervention* 2009;**5**:565–572.
49. Atary JZ, van der Hoeven BL, Liem SS, Jukema JW, van der Bom JG, Atsma DE, Bootsma M, Zeppenfeld K, van der Wall EE, Schalij MJ. Three-year outcome of sirolimus-eluting versus bare-metal stents for the treatment of ST-segment elevation myocardial infarction (from the MISSION! Intervention Study). *Am J Cardiol* 2010;**106**:4–12.
50. Chechi T, Vecchio S, Lilli A, Giuliani G, Spaziani G, Baldereschi G, Montereggi A, Rubboli A, Margheri M, Chechi T, Vecchio S, Lilli A, Giuliani G, Spaziani G, Baldereschi G, Montereggi A, Rubboli A, Margheri M. Mechanisms of late stent malapposition after primary stenting in ST-elevation myocardial infarction: a subanalysis of the selection trial. *J Interv Cardiol* 2009;**22**:201–206.
51. Stone GW, Parise H, Witzenbichler B, Kirtane A, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, McKel M, Lansky AJ, Mehran R. Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up: 2-year insights from the horizons-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol* 2010;**56**:1597–1604.
52. Maehara A, Mintz GS, Lansky AJ, Witzenbichler B, Guagliumi G, Brodie B, Kellett MA, Parise H, Mehran R, Stone GW. Volumetric intravascular ultrasound analysis of paclitaxel-eluting and bare metal stents in acute myocardial infarction: the harmonizing outcomes with revascularization and stents in acute myocardial infarction intravascular ultrasound substudy. *Circulation* 2009;**120**:1875–1882.
53. Mehran R, Brodie B, Cox DA, Grines CL, Rutherford B, Bhatt DL, Dangas G, Feit F, Ohman EM, Parise H, Fahy M, Lansky AJ, Stone GW. The Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. *Am Heart J* 2008;**156**:44–56.
54. Kaltoft A, Kelbaek H, Thuesen L, Lassen JF, Clemmensen P, Klovgaard L, Engstrom T, Botker HE, Saunamaki K, Krusell LR, Jorgensen E, Tilsted HH, Christiansen EH, Ravkilde J, Kober L, Kofoed KF, Terkelsen CJ, Helqvist S. Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 3-year follow-up of the randomized DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction) trial. *J Am Coll Cardiol* 2010;**56**:641–645.
55. O'Riordan M. (2006) *HAAMU-STENT: Less late loss in STEMI patients treated with drug-eluting stents*. http://www.theheart.org/article/750539/print.do.
56. Silber S. Randomisierte Studie zum Vergleich des Paclitaxel freisetzenden TAXUS-Stents vs. unbeschichteten Metallstent bei akutem Myokardinfarkt. *Herz* 2006;**31**:909.
57. Valgimigli M, Campo G, Gambetti S, Bolognese L, Ribichini F, Colangelo S, de Cesare N, Rodriguez AE, Russo F, Moreno R, Piva T, Sheiban I, Penzo C, Prati F, Nazzaro MS, Diaz Fernandez JF, Vassanelli C, Parrinello G, Ferrari R. Three-year follow-up of the MULTIcentre evaluation of Single high-dose Bolus TiRofiban versus Abciximab with Sirolimus-eluting STEnt or Bare-Metal Stent in Acute Myocardial Infarction StudY (MULTISTRATEGY). *Int J Cardiol* 2011; doi:10.1016/j.ijcard.2011.07.106.
58. Stone G, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie B, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Fahy M, Parise H, Mehran R. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 2011;**377**:2193–2204.
59. Fernandez F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso Briales J, Lopez-Mesa J, Fernandez-Vazquez F, Cavlo I, Martinez-Elbal L, San Roman JA, Ramos B. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004; **364**:1045–1053.
60. de la Torre-Hernandez JM, Alfonso F, Hernandez F, Elizaga J, Sanmartin M, Pinar E, Lozano I, Vazquez JM, Botas J, Perez de Prado A, Hernandez JM, Sanchis J, Nodar JM, Gomez-Jaume A, Larman M, Diarte JA, Rodriguez-Collado J, Rumoroso JR, Lopez-Minguez JR, Mauri J. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). *J Am Coll Cardiol* 2008;**51**:986–990.
61. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011;**123**: 1400–1409.
62. Gonzalo N, Barlis P, Serruys PW, Garcia-Garcia HM, Onuma Y, Ligthart J, Regar E. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. *JACC Cardiovasc Interv* 2009;**2**:445–452.
63. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007;**115**:2426–2434.
64. Smits PC, Kedhi E, Royaards KJ, Joesoef KS, Wassing J, Rademaker-Havinga TA, McFadden E. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). *J Am Coll Cardiol* 2011;**58**:11–18.
65. Onuma Y, Serruys PW. Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization?. *Circulation* 2011;**123**: 779–797.
66. Räber L, Kelbaek H, Ostoijc M, Baumbach A, Tüller D, von Birgelen C, Roffi M, Pedrazzini G, Kornowski R, Weber K, Heg D, Matter C, Lüscher TF, Taniwaki M, Meier B, Jüni P, Windecker S. Comparison of biolimus eluted from an erodible stent coating with bare metal stents in acute ST-elevation myocardial infarction (COMFORTABLE AMI): rationale and design. *EuroIntervention* 2012. [Epub ahead of print, 6 February 2012].
67. Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tespili M, den Heijer P, Bethencourt A, Vazquez N, Brugaletta S, Backx B, Serruys P. Rationale and design of the EXAMINATION trial: a randomised comparison between everolimus-eluting stents and cobalt-chromium bare-metal stents in ST-elevation myocardial infarction. *EuroIntervention* 2011;**7**: 977–984.
68. Park KW, Kim CH, Lee HY, Kang HJ, Koo BK, Oh BH, Park YB, Kim HS. Does 'late catch-up' exist in drug-eluting stents: insights from a serial quantitative coronary angiography analysis of sirolimus versus paclitaxel-eluting stents. *Am Heart J* 2010; **159**:446–453 e3.
69. Wessely R, Kastrati A, Schomig A. Late restenosis in patients receiving a polymer-coated sirolimus-eluting stent. *Ann Intern Med* 2005;**143**:392–394.
70. Raber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, Cook S, Moschovitis A, Vogel R, Kalesan B, Seiler C, Eberli F, Luscher TF, Meier B, Juni P, Windecker S. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation* 2011;**123**:2819–2828, 6 p following 2828.
71. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–634.
72. Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Juni P. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;**341**:c3515.
73. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;**291**:2457–2465.
74. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 1997;**315**:640–645.